OVERVIEW

Growth hormone deficiency (GHD) is a complex disorder that can present in childhood or adulthood and results in growth failure along with more serious complications, including delayed bone age, increased adiposity, and systemic symptoms. In this activity, Dr. Vaneeta Bamba reviews the complex management of GHD, from diagnosis through treatment. Dr. Bamba also reviews the wide array of established and novel recombinant growth hormone therapy options, including long-acting growth hormone treatments. Strategies for shared decision making are also discussed, along with recommendations for transitioning patients from pediatric to adult care.

CONTENT AREAS

- Burden of disease
- Individualizing treatment of pediatric disease
- Treatment monitoring
- Adverse event management
- Shared decision making
- Long-acting growth hormone therapy

TARGET AUDIENCE

This activity is intended for a national audience of pediatric and adult endocrinologists, pediatricians, and other clinicians involved in the management of patients with growth/growth hormone deficiencies.

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LEARNING OBJECTIVES

At the conclusion of this activity, participants should be better able to:

- Implement shared decision-making to help patients select a somatropin product based on patient characteristics and needs and product labeling
- Initiate, titrate and monitor somatropin in patients based on patient response and tolerability
- Describe the safety and efficacy of emerging long-acting recombinant human growth hormone therapies and their potential use in clinical practice

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Module 1: Growth Hormone Deficiency Epidemiology, Burden, and Unmet Needs

Overview of GHD

Growth hormone deficiency (GHD) is an endocrine disorder caused by inadequate growth hormone (GH) secretion from the pituitary gland. GHD can be congenital, acquired, or idiopathic, and may be diagnosed in childhood (childhood-onset or pediatric GHD) or in adulthood (adult-onset GHD). Idiopathic GHD is the most common cause of pediatric disease, while adult-onset GHD is most commonly an acquired form of GHD and attributable to pituitary tumors or trauma; although idiopathic GHD has been reported in adults.[1] GHD is a rare disease, reported in between 1:4000 and 1:10,000 children and approximately 1:100,000 adults.[2,3]

GH stimulates the liver and other tissues to produce insulin-like growth factor-I (IGF-I), which facilitates longitudinal somatic growth. Therefore, the most common presentation of GHD in children is growth failure or short stature. The GH-IGF-I axis has also been shown to regulate bone metabolism, protein balance in skeletal muscle, fat mass, and glucose homeostasis.[4] Infants with GHD are at risk for hypoglycemia, and may present with microphallus in boys, prolonged jaundice, and other pituitary defects. In addition to short stature, older children may present with delayed bone age and truncal obesity. Adults are more likely to present with increased abdominal and visceral fat mass, decreased muscle mass, and other systemic symptoms, such as fatigue.[1]

Burden & Treatment

Although short stature is the most commonly discussed outcome of GHD, several other long-term complications have been reported. Infants with hypoglycemia must be treated urgently. When left untreated, patients with GHD may have elevated risk for osteopenia, dyslipidemia, and impaired glucose tolerance.[5] Furthermore, overall mortality risk is increased by 8- to 9-fold in those with childhood-onset GHD and by 2- to 3-fold in those with adult-onset GHD. Adult-onset GHD has a stronger correlation with cancer and cardiovascular mortality, while the increased risk in childhood-onset GHD tends to be due to cancer alone.[3,6] Therefore, early treatment of GHD is strongly recommended both to achieve potential adult height and to reduce the risk of long-term sequelae.[7,8]

GHD is treated with recombinant GH (rhGH), which is currently available only in a daily injectable form.[7,8] Treatment with rhGH has been shown to accelerate growth velocity and normalize growth and stature in children with GHD.[7] In adults, rhGH therapy has been shown to prevent or reverse adverse metabolic effects and improve quality of life.[8] Despite the established benefits of rhGH treatment, nonadherence is common, due to the burden of treatment, discomfort with injections, and poor communication between healthcare providers (HCPs) and patients and/or caregivers.[9]

Module 2: Pediatric Treatment Recommendations

The primary goal of rhGH therapy in children with GHD is to replace the hormone deficiency, which will normalize growth velocity to attain adult height appropriate for genetic potential.[7] Untreated, children with idiopathic GHD reach an average adult height of 4.7 standard deviations (SDs) below the population average (-4.7 SD score [SDS]).[10] In contrast, those who receive rhGH reach an average adult height of -1.0 SDS and an average midparental height of -0.4 SDS.[7] Factors influencing total change in height SDS include midparental height, height change in the first year, height at baseline, duration of rhGH treatment, maximum GH level on stimulation testing, presence of multiple pituitary hormone deficiencies, and birth weight.[11]

Treatment with rhGH is recommended for all children and adolescents who meet the diagnostic criteria for GHD. According to the Pediatric Endocrine Society, GHD can be diagnosed using a combination of clinical evaluation, auxology, and testing for IGF-I and GH. Due to the pulsatile nature of GH secretion and the need for stimulation testing, there is no universally agreed upon cutoff for GH level requiring treatment. Commonly used cutoff values of <5 µg/L and <10 µg/L have been applied in the clinic and in clinical trials.[7] Treatment with rhGH may also be considered for children with idiopathic short stature (ISS), defined as height SDS of -2.25 or lower (≤1.2nd percentile), on a case-by-case basis.[7,12] However, the latter is a controversial indication and should not be routinely applied to all children with ISS.[12] Instead, rhGH treatment for ISS should be based on a shared decision-making approach that incorporates consideration of physical and psychosocial burdens of short stature along with discussion of risks and benefits.[7]

Treatment Considerations

rhGH Dosing

In children, dosing of rhGH is typically dependent on age and weight or body surface area (BSA). Somatropin has been approved at doses of 22 to 35 µg/kg/day, usually administered 7 days per week for a total of 0.16 to 0.24 mg/kg/week.[7] For more detailed information about rhGH dosing by agent, refer to **Table 4.1** in Module 4.

During treatment, monitoring of serum IGF-I levels is recommended as a biomarker of GH exposure. While the target level of IGF-I for maximization of growth outcomes and minimization of risk is unknown, there is evidence that IGF-I levels have a U-shaped relationship with cancer, cardiovascular mortality, and all-cause mortality, indicating that IGF-I levels below or above the normal range increase the risk for adverse events.[13] Therefore, routine IGF-I testing is recommended, and GH dosing should be modified to maintain IGF-I levels within the gender-, age-, and puberty-specific reference ranges provided by the laboratories.

For some rhGH formulations, higher dosing of up to 0.3 mg/kg/week and 0.7 mg/kg/week can be used prepubertally and during puberty, respectively.[13] However, currently, routine dose escalation to 0.7 mg/kg/week is not recommended during puberty due to the potential increase in risk for adverse events and the higher cost of treatment.[7]

The use of higher dosing of somatropin in prepubescent and pubescent children is based on the results of a randomized controlled trial performed in 97 children with GHD. Among those who received the higher rhGH dose of 0.7 mg/kg/week, higher growth velocity and higher

adult height SDS were reported. However, more patients in the higher-dose group had adverse effects consistent with GH excess (eg, ankle swelling or hip pain).[7,14] Currently, routine dose escalation to 0.7 mg/kg/week is not recommended during puberty due to the potential increase in risk for adverse events and the higher cost of treatment.[7]

The Pediatric Endocrine Society recommends initiating rhGH at standard lower doses (eg, 0.16-0.24 mg/kg/week) and then individualizing those doses based on treatment response. Although no standard recommendations for individualization of rhGH dosing are available, clinicians may incorporate the following factors into their decisions to modify rhGH dose[7]:

- Serum IGF-I values
- First-year growth velocity
- Height at treatment initiation
- Duration of treatment
- Peak GH level during stimulation testing
- Midparental height

rhGH Duration

Generally, rhGH treatment should continue until patients achieve adult height or near-adult height, which is defined by very slow growth rate (0.5-3 cm/year) or skeletal maturation (bone age of 14-15 years for girls and 16-17 years for boys). Discontinuing rhGH therapy prior to these height goals is reasonable in some patients based on individualized preferences, risk considerations, and GH axis test results.[7]

Retesting for GH axis normalization can be beneficial to determine if persistent treatment with rhGH is necessary once growth is complete, particularly for patients with idiopathic GHD. In a study of 131 patients with GHD who had completed rhGH therapy and reached adult height, 67% of those with idiopathic GHD had normal GH stimulation test results on retesting.[15] These data suggest that the majority of patients with idiopathic GHD can discontinue rhGH when adult height has been reached.

However, in some cases, rhGH therapy may be continued into adulthood for those with childhood-onset GHD, particularly for patients with congenital GHD, multiple pituitary hormone deficiencies, or other forms of organic GHD. These patients can have body composition changes, osteopenia, and dyslipidemia that may be mitigated by rhGH therapy.[7,8] In one study, retesting of the GH axis at achievement of adult height showed continued aberrant GH secretion in 9 out of 10 children with organic GHD.[15] When transitioning patients with isolated GHD who have completed growth, those with low IGF-1 levels should have the GH axis GH axis retested to confirm continued GH deficiency.[7]

Adverse Events

Data from large postmarketing studies have shown that rhGH treatment has a favorable safety profile during the on-treatment period, and the majority of evidence supports long-term safety as well.[7] Adverse events that merit monitoring and discussion with patients are outlined in **Table 2.1**.

There has also been some concern that rhGH therapy may increase the risk for malignancy; however, the majority of clinical evidence suggests that GH therapy does not increase this risk in patients without known risk factors for cancer. Among those with risk factors for cancer, individualized decision-making regarding the risks and benefits of rhGH therapy is recommended.[16]

Table 2.1. Adverse Events With rhGH Therapy[7]

Adverse event (AE)	Incidence	Monitoring	Notes
Intracranial hypertension	28 per 100,000 treatment-years	Symptoms include severe headache, double or blurred vision, vomiting	• Higher rate reported among those with renal insufficiency, Turner syndrome, and organic GHD • Generally reported during treatment initiation or dose increase • Reversible with discontinuation of rhGH
Slipped capital femoral epiphysis	73 per 100,000 treatment-years	Symptoms include hip and/or knee pain and changes in gait	• Lower frequency in those with idiopathic GHD and ISS • Median time to symptom onset is 0.4 to 2.5 years after treatment initiation
Scoliosis	0.2%	Routine examination for development or progression of scoliosis	• Consequence of rapid growth and not rhGH treatment itself

Shared Decision Making in Pediatric GHD

Shared decision-making (SDM) is a healthcare model in which patients and physicians work together and share information to reach a consensus about preferred treatment.[17] In the context of pediatric GHD, SDM also involves the patient's parents or caregivers.[18]

While there are currently limited data regarding the implementation of SDM in GHD, several theoretical benefits have been identified.[18] Adherence to rhGH therapy is frequently suboptimal, with between 26% and 77% of patients identified as nonadherent.[19,20] Studies have shown that nonadherence is associated with worse outcomes, including less linear growth and slower growth velocity.[21,22] Factors associated with nonadherence include underestimation of the effects of nonadherence, misperceptions regarding disease seriousness, and logistical challenges, such as cost, frequent injections and pain, and the need for routine follow-up medical monitoring.[18] Studies have shown that implementation of SDM may help to address many of these challenges by improving patient and caregiver engagement.

Throughout the GHD treatment journey, there are several opportunities for engaging in SDM. From treatment initiation to transition of care, pediatric endocrinologists should be prepared to involve patients and caregivers in their healthcare. At treatment initiation, providers should work with patients to clarify treatment values and elicit preferences. Helping patients to determine which treatment features they value, and which are less important, can ease decision-making and inform future discussions. The SDM process can help providers individualize discussions and recommendations to better meet patients' preferences and goals.[18]

Summary: Pearls & Pitfalls

- The primary goal of rhGH therapy in children with GHD is to normalize height velocity and attain adult height appropriate for genetic potential. Treatment with rhGH is recommended for all children and adolescents who meet the diagnostic criteria for GHD
- GH dosing should be modified to maintain IGF-I levels within the gender-, age-, and puberty-specific reference ranges provided by the laboratories
- Initiate rhGH at standard lower doses (eg, 0.16-0.24 mg/kg/week) and then individualize those doses based on treatment response
    - Higher doses of rhGH may be considered for prepubertal and pubertal patients with GHD, but AE risk may increase
- Incorporate SDM into patient interactions, particularly for decisions related to treatment and transition of care

Module 3: Adult Treatment Recommendations

Adults with GHD can have childhood-onset or adult-onset GHD. Not all adults with childhood-onset GHD will need treatment—indeed, the majority of adults with childhood-onset idiopathic GHD can safely discontinue treatment once they reach adult height and skeletal maturation. However, a subset of patients with continued inadequate GH secretion and those who develop adult-onset GHD will need ongoing rhGH therapy.[23]

AACE/ACE Guidelines

In 2019, the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) published guidelines for the management of GHD in adults.[23] Compared with children with GHD, adults with new-onset GHD require different rhGH dosing. In patients younger than 30 years, rhGH should be initiated at doses of 0.3 to 0.4 mg/day. Adults aged 30 to 60 years can initiate rhGH at 0.2 to 0.3 mg/day, and those older than 60 years typically start at 0.1 to 0.2 mg/day. Patients with comorbidities such as obesity or diabetes may also benefit from rhGH initiation at lower doses, similar to those used in older patients. Patients with GHD who are transitioning from pediatric to adult care may resume rhGH doses at 50% of the most recent childhood dose used.[23] For all patients, rhGH dose should then be modified to maintain IGF-I levels within age-adjusted reference ranges. Once ideal dosing has been reached, IGF-I testing should be repeated every 6 to 12 months.[23]

For more information about the management of adult GHD, the 2019 AACE/ACE guidelines can be accessed here.

Module 4: Recombinant Growth Hormone Treatments

FDA-approved options for rhGH therapy are outlined in **Table 4.1**. Several formulations of somatropin are available for patients with GHD with a variety of indications, dosing schedules, and delivery devices. In addition, a long-acting rhGH formulation is currently approved for adult GHD, with more options under review by the

FDA for pediatric GHD. Long-acting rhGH therapy options are outlined in more detail in **Module 5**.

Module 5: Long-acting Growth Hormone Treatments

Although daily rhGH therapy is a safe and effective treatment option for GHD, daily injections can be painful for patients, which may result in nonadherence and suboptimal outcomes. Therefore, there has been interest in the development of long-acting GH (LAGH) analogs to decrease injection frequency and thus reduce distress and improve adherence. Currently, somapacitan is the only FDA-approved LAGH and is indicated for adult GHD. Additionally, 2 LAGHs are currently under review for use in pediatric GHD: lonapegsomatropin and somatrogon.[30]

Somapacitan is a somatropin analog with an attached albumin-binding moiety that delays its elimination. The FDA approval of somapacitan was based on the results of the REAL 1 phase 3 study, which enrolled 301 adults with GHD who were previously untreated. Somapacitan was compared with daily rhGH therapy and with placebo. After 34 weeks of treatment, somapacitan significantly improved the primary end point of truncal fat percentage compared with placebo (-1.53%; $P = .0090$). Somapacitan also improved visceral fat and lean body mass compared with placebo. Furthermore, in a 52-week extension period, somapacitan had a similar adverse event profile compared with daily rhGH therapy.[31] Similarly, in previously-treated adults, somapacitan had a comparable efficacy and safety profile to daily rhGH therapy, with no unexpected safety signals.[32] Although somapacitan is approved for use by the FDA, it is not commercially available in the US, as the manufacturer has not yet determined a launch date.[30]

For pediatric GHD, 2 candidates have shown efficacy in late-stage clinical trials. Lonapegsomatropin is an inactive prodrug of somatropin bound to an inert carrier molecule that slowly releases active GH. In early-phase clinical trials, lonapegsomatropin was shown to be safe and effective in children with GHD. These results were supported by recent results from large phase 3 trials. In the phase 3 heiGHt trial, 161 untreated prepubertal children with GHD were randomized to receive lonapegsomatropin or daily rhGH therapy. After 1 year of treatment, lonapegsomatropin increased annualized height velocity compared with daily rhGH treatment (11.2 vs 10.3 cm/year; $P = .0088$).[30,33] The phase 3 fliGHt trial evaluated the efficacy of lonapegsomatropin in 146 children previously treated with daily rhGH for 13 to 130 weeks. After 26 weeks of treatment, mean annualized height velocity was 8.2 cm/year, and mean change in height SDS from baseline was +0.25.[34] In both phase 3 trials, no new safety signals for lonapegsomatropin were reported, and dose titrations of lonapegsomatropin were correlated with IGF-I levels.[33,34] Lonapegsomatropin is currently under review by the FDA for the treatment of pediatric GHD, with a decision expected in June 2021.[30]

Somatrogon is another LAGH that is under development for pediatric GHD. Somatrogon is a derivative of somatropin, with an additional peptide sequence from human chorionic gonadotropin that slows elimination. In a phase 3 trial, 224 prepubertal children with untreated pediatric GHD were randomized to receive somatrogon or daily rhGH therapy. After 1 year of treatment, mean height velocity with somatrogon was noninferior to rhGH therapy (10.12 vs 9.78 cm/year), as was change in height SDS (0.92 vs 0.87). As with other LAGHs, adverse events with somatrogon were comparable with those with daily rhGH therapy.[35] Somatrogon is currently under review by the FDA for the treatment of pediatric GHD, with a decision expected in October 2021.[36]

As LAGHs become available, endocrinologists will have a new treatment option for patients with GHD that has the possibility to reduce distress and improve adherence through less frequent injections. The currently available data suggest that the short-term safety profiles of LAGHs are comparable with daily rhGH therapy. In addition to the need for more long-term studies, monitoring protocols remain unclear: what are the pharmacodynamics of IGF-1 with these newer agents, and how do we interpret these in children with different contributing factors, such as age, sex, and pubertal maturation? Nonetheless, it is likely that LAGHs will prove a useful addition to the current GHD treatment options, and clinicians should be prepared to discuss the efficacy and safety of these agents with patients during the shared decision-making process.[30]

Table 4.1 Available rhGH Formulations for GHD[24-29]

Agent	Description	Indications for GHD	Pediatric dosing	Adult dosing	Dosing schedule	How supplied	Storage
Somatropin formulations							
Genotropin	Somatropin	Pediatric GHD; adults with childhood-onset or adult-onset GHD	0.16-0.24 mg/kg/week	Starting dose of 0.2 mg/day increased by 0.1-0.2 mg/day every 1-2 months OR <0.04 mg/kg/week increased up to 0.08 mg/kg/week at 4-8 week intervals	6-7 daily injections per week	Pen cartridge	Refrigerated
Humatrope		Pediatric GHD; adults with GHD	0.18-0.3 mg/kg/week	Starting dose of 0.2 mg/day increased by 0.1-0.2 mg/day every 1-2 months OR 0.006 mg/kg/day increased up to 0.0125 mg/kg/day	6-7 daily injections per week	Lyophilized powder in vial or pen cartridge	Refrigerated
Norditropin		Pediatric GHD; adults with GHD	0.17-0.24 mg/kg/week	Starting dose of 0.2 mg/day increased by 0.1-0.2 mg/day every 1-2 months OR 0.004 mg/kg/day increased up to 0.016 mg/kg/day	6-7 daily injections per week	Prefilled pens	Refrigerated
Nutropin AQ		Pediatric GHD; adults with childhood-onset or adult-onset GHD	Up to 0.3 mg/kg/week; up to 0.7 mg/kg/week for pubertal patients	Starting dose of 0.2 mg/day increased by 0.1-0.2 mg/day every 1-2 months OR 0.006 mg/kg/day increased up to 0.025 mg/kg/day (patients ≤35 years of age) or 0.0125 mg/kg/day (patients >35 years of age)	Daily injections	Pen cartridge or injection device	Refrigerated
Omnitrope		Pediatric GHD; adults with childhood-onset or adult-onset GHD	0.16-0.24 mg/kg/week	<0.04 mg/kg/week increased every 1-2 months to up to 0.08 mg/kg/week	6-7 daily injections per week	Lyophilized powder in vial or cartridge	Refrigerated
Saizen		Pediatric GHD; adults with childhood-onset or adult-onset GHD	0.18 mg/kg/week	Starting dose of 0.2 mg/day increased by 0.1-0.2 mg/day every 1-2 months OR 0.005 mg/kg/day increased up to 0.01 mg/kg/day	3 alternate days, 6 times per week, or daily	Lyophilized powder in vial or cartridge	Room temperature before reconstitution; refrigerated after reconstitution
Long-acting rhGH formulations							
Sogroya (somapacitan-beco)	Somatropin with albumin-binding moiety attached	Adults with GHD		Initiate at 1.5 mg/week and increase by 0.5-1.5 mg/week every 2-4 weeks, up to 8 mg/week	Once weekly	Pen cartridge	Refrigerated

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